OXYTOCIN FROM THE PITUITARY OR FROM THE SYRINGE: IMPORTANCE AND CONSEQUENCES FOR MACHINE MILKING IN DAIRY COWS

Rupert M. Bruckmaier
Veterinary Physiology, Vetsuisse Faculty University of Bern
Bern, Switzerland

Introduction

Oxytocin is a neuropeptide hormone which is involved in a number of processes related to reproduction such as mating, delivery, mother-offspring-bonding, and milk ejection. Oxytocin was first detected in 1909 by Henry Dale (UK) as an extract from the pituitary that facilitates the process of delivery. From this effect the name of oxytocin is derived (Greek: *okytokos* = quick birth). Oxytocin is released from the posterior pituitary in response to stimuli transmitted via the hypothalamus. It was the first peptide hormone to be sequenced and artificially synthesized (du Vigneaud et al., 1953). Vincent du Vigneaud (Cornell University) received the Nobel Prize of Chemistry for this work in 1955. Since then oxytocin is available as a medicinal product for i.m. or i.v. injection to support delivery and milk ejection in animals and human in case of insufficient endogenous release. Within the mammary gland the main action of oxytocin is the control of milk ejection and thus the availability of milk for the offspring or the milking machine. Its timely and adequate release is crucial for a successful milking process.

Macroscopic Structure of the Udder and Availability of Milk before Milk Ejection

Mammary glands of all mammalian species including dairy cows consist of secretory tissue, and a system of milk ducts and cisternal cavities. The secretory tissue is based on alveolar structures containing secretory epithelial cells and myoepithelial cells which contract in response to oxytocin. The alveoli are connected via small milk ducts with the larger milk ducts, cisternal cavities, teats and the gland orifice. Between the events of milk removal by suckling or milking, milk accumulates in the gland and is stored in these compartments. While the milk stored in the alveoli and small milk ducts is fixed by adhesive forces (alveolar milk), the milk in the larger ducts and cavities (cisternal milk) is only prevented from draining off the gland by the teat canal smooth muscles. Thus the cisternal milk can immediately be removed through the milking vacuum (negative pressure) while the alveolar milk is not available before it is actively shifted into the cistern by a positive pressure on the alveoli through myoepithelial contraction in response to oxytocin. The amount of cisternal milk differs tremendously between species from 0 (e.g. sow) to up to 80 % (goat). In dairy cows the cisternal fraction reaches a maximum of 20 to 30 % at 10 to 12 hours from previous milking (reviewed by Bruckmaier & Blum, 1998). During the first hours after milking some refill of the alveolar tissue with newly secreted milk is needed before milk increasingly accumulates in the cistern (Knight et al., 1994). Consequently, at short intervals between milkings, and in late lactation there is no or only little cisternal milk available to bridge the time until oxytocin release and alveolar milk ejection (reviewed by Bruckmaier & Blum, 1998).

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Udder Stimulation, Oxytocin Release and Milk Ejection

The neuropeptide oxytocin is produced in the hypothalamus and stored in the posterior pituitary until released into blood circulation. Its concentration in blood is extremely low as compared to other hormones (1-5 pg/ml (= 10^{-12} g/ml) basal values). During machine milking, oxytocin is released via a neuroendocrine reflex mainly in response to tactile stimulation of the teats and other areas of the udder. Alternatively, a more pronounced oxytocin release can be achieved by tactile vaginal or cervical stimulation, potentially a method to be used if the response to udder stimulation is insufficient (disturbed milk ejection). Other types of stimulation such as acoustic or visual stimuli do obviously exist in some species but have never been approved in dairy cows. Depending on the type and intensity of stimulation oxytocin increases to levels of 10-100 pg/ml in dairy cows. However, the effect of oxytocin with respect to milk ejection is not related to the extent of oxytocin release. It has been demonstrated in dairy cows that surmounting a threshold of approx. 10 pg/ml induces a maximum milk ejection. Consequently, there are no special requirements for the intensity of stimulation of the mammary gland to induce a sufficient oxytocin release for maximum milk ejection (Weiss et al., 2003). A minimal but sufficiently intensive stimulation would be e.g. cluster attachment without pulsation (in liner-closed position), followed by manual stimulation or stimulation by the normal liner movement or vibration in liner closed position. Beyond that calf suckling and vaginal stimulation induces a more pronounced oxytocin release. Only supraphysiologically high oxytocin blood concentrations which can only be achieved by exogenous administration of oxytocin at a high dosage, can induce an even more efficient milk ejection to remove also the so-called residual milk, a portion of 5-20 % of the total milk which remains in the udder under physiological conditions (reviewed by Bruckmaier & Blum, 1998).

Lag Time to Induce Milk Ejection

In dairy cows, elevated blood concentrations of oxytocin in the jugular vein can be measured within 30 s after the start of stimulation, independent of the lactational stage, season, or other potential factors of influence. While the oxytocin release in response to tactile stimulation underlies almost no timely variation, the lag time until occurrence of alveolar milk in the udder cistern in response to endogenously released or injected oxytocin varies widely. It has been demonstrated that the relative degree of udder filling is the main factor to affect this lag time, and with decreasing degree of alveolar filling the lag time until milk ejection increases. Differences are due to different lactational stages or due to different intervals between milkings which is most relevant at more than 2 x daily milking (Bruckmaier & Hilger, 2001) or at robotic milking (Dzidic et al., 2004a, b). Alveolar milk reaches the cistern at about 40-50 s after the start of tactile stimulation in full udders, and this lag time can reach up to 3 min in udders with a very low degree of filling. This variation is most likely caused by a different degree of myoepithelial contraction which is necessary until milk is pressed out of the alveoli (Bruckmaier & Hilger, 2001).

Requirements of Prestimulation

It is generally accepted that a transient milking on empty teats at the full load of vacuum and pulsation causes damage of the teat tissue, and may prolong the milking process after a delayed

milk ejection has been induced by the teat cup liner (reviewed by Bruckmaier & Blum, 1998). Prestimulation starts the milk ejection process while simultaneously removing no or only small amounts of milk. Because special requirements for the intensity of a tactile stimulation do not exist, stimulation can be manually through cleaning the teats and udder and stripping the first squirts of milk, or mechanical through the liner while reduced pulsation vacuum keeps the liner closed, or at a reduced vacuum in the milk tube and short b-phase until alveolar milk is available. Milking at normal pulsation without previous teat preparation causes a separate removal of cisternal and alveolar milk fractions (bimodal milk flow) which can cause a reduced milk flow rate and in some cases insufficient udder emptying and hence an increased risk of mastitis through teat tissue damage and increased residual milk.

Prestimulation usually lasts for 30 to 60 seconds, and at very low udder filling even a longer prestimulation can be beneficial (Weiss & Bruckmaier, 2005). Prestimulation can be permanent for 30 to 60 s (or even longer at low degree of udder filling), but can also be split into a short tactile stimulation (minimum 15 s), followed by a latency period up to 45 s (Kaskous & Bruckmaier, 2011). Due to the fast decline of oxytocin after the end of stimulation a longer latency period is not recommended because the myoepithelial contraction will be released at latest at > 2 min of latency period.

Continuous Oxytocin Release and Milk Ejection during Milk Removal

Milk ejection in dairy cows continues throughout milking because milk ejection does not imply a complete shift of alveolar milk into the cistern during prestimulation or at the start of milking (reviewed by Bruckmaier & Blum, 1998). A continuously elevated concentration of oxytocin is therefore necessary during the entire milking process which is provided by the stimulatory effect of the liner. The short halflife of oxytocin in blood circulation of only 2-3 min causes an almost immediate cessation of milk ejection when the respective tactile stimulus is terminated. In nature, this allows a milk ejection according to the needs of the suckled offspring. During machine milking the goal is a complete emptying of the udder, and it is therefore important that the cluster and liner do not cause any pain to the animal which could lead to a pre-term cessation of oxytocin release and milk ejection.

The continuous character of milk ejection is responsible for the continuous change of milk composition during the course of milking. While milk protein and lactose remain almost constant, the milk fat content increases continuously from about 1 % in cisternal milk up to >10 % in the final alveolar fraction. Somatic cell counts are mostly high in cisternal milk, lowest in the first alveolar fraction, and increase continuously during the further course of milking. This fact must be considered for analytical milk sampling (Sarikaya et al., 2005).

The Role of the Sympathetic Nervous System and Adrenaline for Milk Removal

Catecholamines such as adrenaline and noradrenaline rather stimulate than inhibit the release of oxytocin in response to teat stimulation (reviewed by Bruckmaier & Blum, 1998). Experimentally, only a supraphysiological amount of adrenaline causes an extensive contraction of milk duct smooth muscles and despite alveolar contraction alveolar milk cannot be shifted to

the cistern. In practical farming these conditions have never been observed, and a role of adrenaline in the inhibition of milk ejection is very unlikely.

However, adrenergic receptors of the smooth muscles in the milk duct system are controlling the efficiency of milk transport through the ducts to the cistern during the continuous milk ejection and hence influence the availability of cisternal milk and milkability (Roets et al., 1989; Inderwies et al., 2003a, b). Also the teat sphincter smooth muscle tone is under sympathetic control (Lefcourt, 1982). Changes of the teat sphincter tone were shown to barely cause changes of milk flow out of the cistern induced by the vacuum during machine milking (Bruckmaier et al., 1997). However, a low sympathetic tone of the teat sphincter muscles increases the likelihood of milk leakage ("incontinentia lactis") which can be particularly high shortly before milking, e.g. when the vacuum pump is switched on. The leaking milk is only cisternal milk and is not related to oxytocin release and milk ejection (Rovai et al., 2007).

Lack of Oxytocin Release and Disturbed Milk Ejection

Disturbed milk ejection can occur in primiparous cows during the first weeks postpartum, in unfamiliar surroundings (e.g. after the changeover to a new milking system), or during estrus (reviewed by Bruckmaier & Blum, 1998). Disturbed milk ejection was shown to be regulated at the level of the central nervous system and is expressed via reduced or totally lacking release of oxytocin in response to the milking stimulus. A field study in Switzerland which included > 67,000 cows showed that about 4 % of the dairy cow population had bad milkability, mostly due to disturbed milk ejection (Belo et al., 2009). The percentage of affected animals was similar in Holstein, Brown Swiss, and Simmental x Red Holstein breeds. Any relationship of disturbed milk ejection with genetic strains of the animals, or to special housing and milking conditions was not found (Belo et al., 2009). In a representative sample the reason for the bad milkability was experimentally demonstrated to be due to insufficient oxytocin release in 69 % of the cows under suspicion (Belo et al., 2009).

While it was demonstrated that adrenaline is not responsible for disturbed milk ejection in practical farming it remains unclear which factors are controlling the inhibition of oxytocin release as the main cause of disturbed milk ejection during machine milking. Some results indicate that endogenous opioid peptides, possibly together with cortisol, are involved in the inhibition (reviewed by Bruckmaier & Blum, 1989). It was experimentally shown that morphine inhibits the release of oxytocin during milking, and the opioid antagonist naloxone increases the milking-related release of oxytocin in cows with non-disturbed milk ejection (Tancin et al., 2000). Naloxone had, however, no clear effect on the milking-related release of oxytocin in cows with disturbed milk ejection (Macuhova et al., 2002). Disturbed milk ejection is mostly treated with exogenous oxytocin injected before each milking (details see next paragraph). An alternative method which works in most cases is vaginal or cervical tactile stimulation immediately before milking. This method can be used in a tie stall but is obviously not suitable in most parlor or robotic milking systems.

Use of Exogenous Oxytocin

Most of the animals with disturbed milk ejection are treated with oxytocin from the syringe before each milking (Belo et al., 2009). Besides that, oxytocin injection before milking can be used in mastitis therapy (Knight et al., 2000), or to increase milk production (Nostrand et al., 1992).

Oxytocin is injected either intramuscularly (i.m.) or intravenously (i.v.), mostly at a dosage which results in plasma concentrations far beyond the physiological level. While oxytocin levels after the cessation of release from the pituitary drops to baseline within minutes due to the short halflife of 2-3 min (Belo et al., 2010) oxytocin remains elevated for hours especially after i.m. injection because of its continuous release from the muscle tissue into blood circulation (Macuhova et al., 2004). Besides a complete udder emptying at milking mostly including residual milk this causes a continuation of milk ejections during the first hours after milking, and an early accumulation of cisternal milk which would start only at 4-5 hours after milking under regular conditions (Macuhova et al, 2004). Both, more efficient emptying of the udder, and continued milk ejection may be the basis for a reduced autocrine feedback inhibition of milk secretion and thus increased milk production (Collier et al., 2012).

Often oxytocin from the syringe is used chronically at least for a period of time. This treatment has several consequences which need to be considered. Very obvious is the effect that cows become afraid from voluntarily entering the parlor because they expect the injection. Thus it was observed in farms with frequent oxytocin use that many cows had to be driven into the parlor and that many animals started to defecate while present in the parlor. Because milk ejection and milk removal is sensitive to stress reactions it is obvious that the treatment does not support the required wellbeing and calmness during milking.

Besides the observed behavioral changes of the animals there are also physiological effects of chronic oxytocin treatment. Already after one week of i.m. oxytocin injection (30 I.U.) to cows with normal milk ejection before the start of the treatment led to a dramatic reduction of udder emptying if oxytocin injection was not applied (Bruckmaier, 2003), i.e. cows become addicted to the treatment, and it takes about 2 days until milk removal normalizes without the use of oxytocin (Bruckmaier & Macuhova, unpublished). Because a transient only partial udder emptying causes an increased risk for intramammary infection, and irreversible decrease of milk production, the treatment can basically not be stopped before dry off.

Unexpectedly the treatment with exogenous oxytocin increased the milking-related release of oxytocin from the pituitary, obviously based on a positive feedback mechanism of oxytocin on its own release (Macuhova et al., 2004). Despite a normal oxytocin release after cessation of the treatment, there was a pre-term stop of milk ejection during milking which led to the observed incomplete udder emptying (Macuhova et al., 2004). Most likely a desensitization of the oxytocin receptors of the myoepithelial cells is responsible for this effect. Thus the chronic use of oxytocin at a high dosage should be avoided whenever possible.

In a recent study we could demonstrate that much lower amounts of oxytocin injected i.v. are capable to induce complete milk ejection in animals with disturbed milk ejection (Belo &

Bruckmaier, 2010). The required exceedance of the oxytocin threshold to induce milk ejection throughout the entire milking process can easily be reached by dosages < 1 I.U. of oxytocin. The needed dosage depends of the time needed to empty the udder, i.e. of the milk yield and anatomical milkability of the animal. The response phase was 2-3 min, and 3-5 min at oxytocin dosages of 0.2 I.U. and 0.5 I.U., respectively (Belo & Bruckmaier, 2010). By these treatments or even up to 1 I.U., oxytocin plasma concentrations decreased to baseline within 20 min, and an effect of addiction to the treatment is most likely avoided. Because commercial oxytocin products are only available at concentrations of 10 I.U./ml or even 20 I.U./ml, the product must be diluted in sterile physiological saline solution, e.g. 1:100. Doing so, 0.2 I.U. or 0.5 I.U. can be injected in 2 ml or 5 ml of sterile solution, respectively (Belo & Bruckmaier, 2010).

In conclusion, oxytocin from the syringe should only be used if absolutely necessary, and an alternative treatment by vaginal stimulation should be considered if suitable for the farmer.

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